INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 97-CH-0076 PRINCIPAL INVESTIGATOR: Constantine A. Stratakis, M.D.

STUDY TITLE: Tumors of the Pituitary Gland and Associated Conditions: A Genetic Investigation

Latest IRB Review: Continuing Review 2/4/04
Latest Amendment Approved: Amend D 1/12/03
Consent Form 2

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

You or your child have (has) a tumor in one of the glands of the human body that produce hormones, called the "pituitary gland". The cause of this tumor is unknown, but some times these tumors can run in families. One way of finding out what caused this tumor, is to study the blood of your child and the tissue of the tumor. This is why we are doing this study. At the National Institutes of Health, we will also try to find the kind of tumor your child has, if this is not already known. When we know the type of tumor, we will offer treatment that can be done here or suggest other places where treatment can be offered. For most pituitary tumors, this is not different from the standard medical evaluation and treatment that would be available at other hospitals in this country. The only research part of this study is related to the genetic cause of these tumors and is explained below.

An additional research objective of this study includes the evaluation of a new scan (imaging technique) for the earlier and more accurate detection of pituitary tumors; this technique is called (SPGR-MRI) and is explained in details below.

If your child has Cushing syndrome, another physician, a pediatric endocrinologist, Dr. Deborah Merke, will ask you whether you and your child are interested to participate in a separate part of the study. This part of the study will

evaluate the psychological changes that may be present in your child as a result of Cushing Syndrome, if this is the diagnosis for your child. If you and your child decide to participate in this part of the study, you will be asked to sign a separate consent form and undergo testing that will last approximately 3 hours. This part of the study will go on for five years with annual evaluation and testing.

What is this study about?

The purpose of this study is to find out the type of tumor your child has and learn more about what caused it.

What is regular medical care and what is research in this study?

a) Routine Medical Care

In order to find out what kind of tumor you or your child have (has), we may need to do a number of blood, urine and X-ray tests. We will not repeat any of the tests that you already had, unless there is a need to do them because a long time has passed since they were performed or because their results were unclear. Based on the results of these tests, we will make a presumptive diagnosis about the type of tumor, and we will discuss the various possibilities for treatment. If surgery is needed, it can be performed here, at the NIH, by an experienced pituitary surgeon and his team. If medical or radiologic treatment is indicated alone or in combination with surgery, we will discuss with you the various options and what is available at the NIH. Radiation treatment, for example, is currently not available by our department. If you wish, after surgery, you or your child will be followed by our endocrinology outpatient clinic along with your endocrinologist. Following this first year or after your discharge from the hospital the first time (if you do not wish to be followed by our clinic), we will make suggestions and, if possible, arrangements for you or your child's care and follow up elsewhere. If your child has Cushing syndrome, he/she may be followed up by our clinic for up to 5 years, if you agree to participate in the psychological assessment part of our study.

No tests, other than the ones described below in the "research" section, will be obtained for research purposes only during your stay in our hospital. If you wish, however, to participate in other research studies performed at the NIH, please let us know, either before your admission to the hospital or during your stay here.

This study serves our Institute (the National Institute of Child Health and Human Development, which is part of the National Institutes of Health) as training tool for our physicians-in-training and students. Most of the every day care will be provided by these physicians, who are supervised by Dr. Stratakis and the other investigators of this study.

b) Research Part of the Study

The research components of this study have the following objectives:

-To confirm the type of tumor by clinical studies and by examining the tumor tissue itself. This part of the study will only include patients who require surgery for standard treatment of the tumor. The type of tumor will be verified when the tumor is taken out at surgery and the tissue is examined in the laboratory. Part of the tumor will be stored for DNA studies (see below).

-To examine the usefulness of new imaging techniques in the recognition and management of pituitary tumors. We would like to develop new imaging techniques to detect small pituitary tumors. If the tumor is small (called "microadenoma"), we will ask you whether you would like to participate in the evaluation of a new magnetic resonance

imaging (MRI) scan technique. This is like the regular MRI but it allows for better computer resolution. Although you or your child will not see or feel anything different, the second MRI will follow the first, regular MRI (that we need to obtain as part of the standard medical evaluation for pituitary tumors) and this examination will prolong significantly the time you or your child will spend in the MRI examining room. You may not want yourself or your child to participate in this part of the study; please let us know, if this is your wish, and we will not obtain this second MRI.

-To examine the effect of cortisol secretion on psychology and cognition; this study is limited to pediatric patients with pituitary tumors causing Cushing disease. If your child has this disease, another physician, a pediatric endocrinologist, Dr. Deborah Merke, will ask you whether you and your child are interested to participate in a separate research study. This study evaluates the psychological changes that may be present in your child as a result of Cushing Syndrome, if this is the diagnosis for your child. If you and your child decide to participate in this part of the study, you will be asked to undergo testing that will last approximately 3 hours. These tests consist of various questionnaires that you will be asked to complete. There is no additional blood testing in this part of the study, but there is an additional MRI of the brain that we will need to perform to correlate any changes in your child's behavior with brain anatomy and function.

-To find out what caused the pituitary tumor by studying the "genetics" of the tumor. To do this, we will test your blood or the blood of your child and the tissue of the tumor, if that is available. We will then study the DNA in the tumor and the blood cells. DNA is the substance that contains the genes, the units that determine inheritance. If we think that a disease that makes you or your child more likely to have tumors runs in your family, we will ask you to help us draw a family tree and collect blood from you and your relatives. We will compare the DNA from various family members to see if we can find something in common among the people who have tumors. This will help us to find the problems in the genes.

-The DNA and tumor samples will be stored with codes assigned to them in our laboratory at the NIH. The principal investigator of the study has the key to the code that identifies the patient and links him or her to a particular sample. Occasionally, tumor samples sent from outside NIH will have a name identifier – they will also be assigned a code. All these samples will be stored at the NIH and not used for any other studies without your permission. Coded samples may be used by other scientists, who collaborate with the investigators of this study, in the effort to identify the genetic defects involved. These investigators will not have access to the names that identify the specimens that are used in these research experiments.

You do not have to participate in the research parts of the study, if you do not want to.

What we will do

We will contact you by phone or mail, after your endocrinologist has told us about yours or your child's disease. We will discuss with you and your physician whether you are (or your child is) eligible for the study.

If you take part in the study, you or your child will be admitted to the hospital for the needed testing. You will have to spend approximately one week in the hospital undergoing tests, if these are needed. If this is the case, you will

return at a later time for surgery. If few or no tests are needed, and surgery is recommended, you will be admitted for two weeks for the surgery. Most often, the studies to find out the type of the tumor, and the surgery or other treatment, will be done in two different hospitalizations.

Once admitted to the hospital, we will do the following:

(1) Medical history: We will ask you and/or your child about medical conditions associated with diseases of the pituitary gland. These include skin problems, tumors of other glands and other related diseases. We may ask you to help us draw a "pedigree" (this is a medical term for a special diagram of your family tree). We may also ask for additional medical records for problems that you had in the past, and we may need to contact your physicians. We will ask you to sign a paper to allow us to see these records.

(2) Physical examination: We will examine you/your child with clothes off. The examination will include body measurements, such as the distance between the eyes and the head circumference, and your child's height and weight.

(3) We may ask you to collect urine over twenty-four or more hours, to measure hormones in the urine.

(4) X-ray and other studies: A non-x-ray scan (MRI) of the head that includes the pituitary gland will be obtained, if you or your child has not had one recently. Other studies, such as a computed tomography (CT) of the adrenal glands may be need to be obtained, if not already done. In both tests, a dye ("contrast" material) may need to be given through a vein. This procedure will be explained to you and/or your child in detail by the doctor who will be doing it (a radiologist) and a separate consent will be obtained.

(5) We may ask that you/your child is photographed in your/his/her underwear. This is frequently done by physicians, especially endocrinologists because pictures are the best way of documenting the physical changes that take place with pituitary tumors; also to document the growth and development of a child. These pictures will not be used for any publication without your written permission.

(6) Blood testing: To find out the type of tumor, before surgery or any other treatment is offered, we may need to do some blood tests. These tests will be obtained only if you or your child did not have them before, or if the tests were performed a long time ago, or if they were not informative.

Generally, when such a test is performed in our hospital, a small plastic tube ("catheter") is placed in a vein in the forearm. This requires a stick with a needle, and hurts for a minute or two. Then it will stop hurting. We will put a special cream on your child's arm called EMLA one hour before drawing blood to reduce the pain from the needle's insertion.

We will try to obtain all necessary blood tests through this one plastic tube, which will remain in place for as long as is needed for the testing.

(7) Material used for research

From the same tube (the "catheter"), we will get a small amount of blood [about 2 tablespoons (30 (8ml)] for genetic analysis. We will use this to get DNA.

We will also be using part of the tissue from the tumor that will be obtained during surgery, as explained above.

We will look at the results of the imaging studies (the MRI scans and others) and evaluate them in order to come up with recommendations for better imaging of the pituitary gland.

If your child has Cushing disease (syndrome) and you have decided to participate in the part of the study described above that is co-ordinated by Dr. Merke (evaluation of psychological changes in children with Cushing Syndrome), we will use the information collected from the questionnaires and the MRI of the brain to evaluate behavior and other changes during the course and after the cure of Cushing Syndrome in your child. This psychological testing will only be performed once prior to surgery for Cushing Syndrome and, after that, every year for five years, if cure of Cushing Syndrome has been confirmed.

A list of the tests follows (they will be explained to you in detail by Dr. Merke, or one of the people working with her):

1. Wechsler Intelligence Scale, 3rd edition
2. Woodcock Johnson Achievement Tests
3. California Verbal Learning Test
4. Trailmaking Test
5. Bender-Gestalt Test
6. Boston-Naming Test
7. Behavior Assessment System for Children (BASC)
8. Diagnostic Interview Schedule for Children (DISC)
9. Continuous Performance Test

This evaluation will take approximately 3 hours. An additional part of this evaluation, is the quality of life for you and your child, before and after surgery for Cushing syndrome. Katherine Obunse and/or Meg Keil will ask you (and your child) to complete one additional questionnaire along with a symptoms' list for Cushing syndrome; this additional part will only take 20-30 minutes.

As with any of the research parts of the study, you do not have to participate in any of the above components – if you feel that you or your child should not go through this additional evaluation please let us know.

(8) Follow up after the completion of all medical studies

After all the medical testing, when we know the type of tumor you/your child has, several options will be discussed with you. We will report the results of the medical tests to you and your doctor.

To decide how the tumor should be treated, the findings will be presented to our neurosurgery service. If they decide that surgery is the best treatment option, we will discuss it with you, and offer surgery here at the NIH. In most cases, this surgery can be done through the mouth ("transsphenoidal surgery"). If the tumor is very large, the surgery may be done through the forehead. The neurosurgery doctors will explain the surgery to you and your child. Separate consent will then be obtained for this. If a surgery is not successful, repeat surgery may need to be done. This will be discussed with you by us and the neurosurgeon. Complications of the surgery are briefly listed in the "risks" section of this consent form; however, they will be extensively discussed with you by us and the neurosurgeon. Surgery is not always able to cure a tumor. Tumors that cannot be cured by surgery may be candidates for radiation treatment but this is not offered at the NIH under this research protocol.

If you/your child has a specific type of tumor called "prolactinoma" he/she may be able to be treated with medicine taken by mouth, instead of surgery or radiation treatment. For the medical treatment and the follow-up after surgery, your child can be seen for one year as an outpatient at the NIH Clinical Center Pediatric Endocrinology Outpatient Facility, either in the day hospital or the clinic. Before, or at the end of this year, at your request, we will make arrangements for the continuation of your care by your pediatrician or endocrinologist.

(9) Alternatives to treatment provided at the NIH

The evaluation and treatment that you/your child will receive at the NIH can be found at other hospitals.
At any time, after your entry into the study, you or your child may decide to stop coming to the NIH. We will provide you with all the information gathered here about your (or your child's) health and talk to the physicians wherever you may decide to go, to ensure proper follow-up treatment. Please let us know, at any point, of concerns you might have, or of any questions that may arise.

(10) Research conducted in the course of this study and its effects on your decision to receive care by another hospital

The only research blood tests in this study are the blood that we will obtain for genetic testing from your child (and the family if needed). In addition, we will examine genetically the tissue from the tumor that will be obtained during surgery, if surgery is done.

If you decide to go somewhere else for treatment, you can still participate in this study, by allowing us to contact the doctors that will be taking care of your child and make arrangements for us to receive part of the tumor tissue that will be taken out.

If you allow us to obtain the second MRI scan (SPGR-MRI), we will be able to compare the latter with the regularly obtained MRI scan and determine whether the new technique is more helpful in the detection of pituitary tumors.

If your child has Cushing Syndrome and you decide to go ahead with the psychological testing described above, this testing will provide the researchers with information on the psychological changes associated with Cushing Syndrome in children. Diagnosis of these changes may lead to effective treatments and avoidance of permanent effects in the personality and behavior of the child.

(11) Results of "genetic testing"

As with the results of the medical testing, we will inform you, your child and your physician of the results of our genetic testing. If you do not wish to be informed of these results, please let us know, and we will not release this information.

The information becomes part of your child's medical record, which is protected by "the Federal Privacy Act". However, this Act allows release of some information from your medical record without your permission, for example, if it is required by members of the Congress, law enforcement officials or other authorized people. Your or your child's ability to obtain insurance could be affected if our study results show a gene that causes tumors is found in your or your child's blood. Theoretically, this could also make it harder to find a job, if an employer knew about the problem.

If from our clinical evaluation we find a genetic condition that is inherited (for example Multiple Endocrine Neoplasia (MEN), Carney complex, or other genetic syndrome), we will discuss with you the implications of this, and your risk for having children with these disorders. We can reveal DNA testing results that have been obtained at NIH, only if our

laboratory and other NIH facilities are approved for this procedure, according to recent regulations. For some of these genetic diseases, that we have not been approved to provide testing results, molecular testing is available in approved laboratories; if your desire is that you undergo this testing in an approved laboratory, we will provide the necessary information. However, if any charges are involved, these are your responsibility.

If we learn anything else about your or your child's medical condition during the course of this study, we will inform you, your child and your doctor(s). Please also note that our DNA studies will only relate to the inheritance of genetic condition associated with pituitary tumors. We will not test for any other genetic or acquired conditions without your assent and written consent.

Results of genetic (experimental studies) of the tissue derived from the tumor that will be taken out from your child will not be discussed and will not be part of the medical record, unless they have some relationship to your or your child's health. Most of these studies are of interest to the scientists that are doing them and may provide useful information for research and perhaps health care in the future, but they are of no use to current medical care.

By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights please contact the principal investigator (Dr. Stratakis) or your primary and referring physician (if you are being seen at another institution).

Other risks or discomforts from participation in this study

1. It is inconvenient to give information about medical and family history and to have physical examination and any testing needed to find out about a pituitary tumor.

2. Total blood drawing will not exceed the NIH safety limit.

Blood drawing can be uncomfortable too; this includes the pain of the needle-stick, the slight chance of fainting, the possibility of a bruise, and the small chance of an infection at the needle puncture site. You or your child will receive appropriate treatment for any complications of this sort.

There may be additional risks from the medical tests that will be obtained here at the NIH; these will be explained to you and your child in detail, if your child needs such a test. They include headaches, blood pressure changes, rashes due to allergy, and other symptoms. A potentially life-threatening condition is called "apoplexy", which is a situation of shock that occasionally leads to coma; it occurs extremely infrequently during pituitary gland testing and sometimes happens with large tumors. During testing your child will be closely monitored for any symptoms of this condition. Treatment will be offered immediately in such an event.

3. The additional MRI scan of the pituitary gland will be performed in the same room as the regularly offered MRI; although you/your child will not see or feel anything different, the time required to stay in the MRI room will be prolonged and, if sedation was needed for the first MRI, sedation will also have to be prolonged. Staying in the MRI room with all its noise and large equipment may be uncomfortable for young children, who, in addition, have to stay still for the proper completion of the procedure. Moreover, sedation has its own risks (respiratory and others) which will be explained to you by the anesthesiologist and radiologist that will be there during the procedure. If sedation is needed, another consent form will be obtained at the time of the procedure by the physician who will be administering it.

4. If surgery is needed, there are possible complications of the various procedures that may be performed, that include infection, blindness and, rarely, death. These will be explained to you in detail by us and our neurosurgeon in a separate consent form.

5. It takes approximately three hours to complete the psychological testing for patients with Cushing Syndrome. This is often uncomfortable. Your participation in our study does not mean that you have to participate in other studies conducted at the National Institutes of Health; you may elect to participate, however, in this additional study, as well as other studies at the NIH.

6. If an adverse event occurs during the course of this study it will promptly be reported to the monitoring bodies that have been established for that purpose at the NIH.

Benefits

1. If you wish, we will inform you about the results of our genetic investigation. We will tell you and your child, if we find that your family is at risk for developing a pituitary tumor due to a genetic disease.

2. If you or your child does have a genetic condition associated with pituitary tumors, or if we discover that you are at risk for developing any of these diseases or their complications, we will discuss with you the chance that your other children or your child's children could have the same health problems. If appropriate, we will refer you for additional genetic counseling.

3. If there is a tumor in the pituitary gland, you/your child can receive appropriate medical or surgical treatment, and then follow-up for one year at the NIH.

4. There is preliminary evidence that the second MRI that will be obtained in patients with smaller, usually undetectable tumors, improves our ability in detecting those tumors. If this second MRI shows the tumor in your child, that will improve yours/your child's chances for cure from that tumor, by guiding the surgeon to the right place in the pituitary gland for resection of the tumor.

5. The knowledge derived from this study may give us a better understanding of pituitary tumors and other conditions associated with them, eventually leading to better treatments and better ways to detect or even prevent such tumors.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, , contact the Principal Investigator, Constantine A. Stratakis, M.D.; Building 10, Room 10N262, Telephone: (301) 496-4686, or Meg Keil, RN, PNP (301-4961531).

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 13, 2004 THROUGH FEBRUARY 13, 2005.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____